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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/625,573	CHARO ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with **traverse** of Group II (Claims 2-19) in Paper No. 17 (21 April 2003) is acknowledged. This is found persuasive. Applicant's request to rejoin Groups I and III into a single group and the rejoinder of Groups II and IV into a single group is hereby granted. The restriction requirement, after the rejoinder now stands at two Groups. Group A (Groups I and III rejoined) drawn to claims 2-19 (each in part) to SEQ ID NO: 1 and 2 and Group B (Groups II and IV rejoined) drawn to claims 2-19 (each in part) to SEQ ID NO: 3 and 4. The remaining requirement is still deemed proper and is therefore made FINAL.

2. Concerning claims including in Group B (Group II and IV rejoined), claims 2-19 regardless of whether drawn to making the antibody, the cell line which produces said antibody, or the compositions of said antibody, are all included in Group B and will be examined. The restriction requirement is drawn specifically to the SEQ ID NO to which said antibody is directed.

Information Disclosure Statement

3. The information disclosure statement filed 15 February 2001 (Paper No. 10) and 15 February 2001 (Paper No. 15) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The references were also absent from the parent Application 08/446669. It has been placed in the application file, but

the information referred to therein has not been considered. The references listed therein may be provided along with the response to this Office Action with no additional fee.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: it claims domestic priority to 08/182962 filed 13 January 1994. This application is not listed on the Application Data Sheet nor is it disclosed in the first line of the Specification. In addition, USPTO records to do not show this application to be in the continuity data of the instant application. Clarification of this issue is requested.

Drawings

5. The drawings are objected to because Figures 1, 2, 3, 4, and 7 contain multiple subcomponents (i.e. "1A", "1B") which are not described in the Specification. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

6. The disclosure is objected to because of the following informalities: missing space "SciUSA" (pp. 30 line 20). Appropriate correction is required.

Claim Objections

7. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).Misnumbered claims **1-18** been renumbered **2-19**. The claim dependencies have also been corrected.Claims **2-19** are objected to because of the following informalities: recite non-elected matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims **3-19** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *antibodies that bind SEQ ID NO: 4 or the polypeptide encoded by SEQ ID NO: 3*, does not reasonably provide enablement for *antibodies that bind polypeptides with at least 90% or 95% homology to SEQ ID NO: 4*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

11. The above invention is drawn to a method of making antibodies that bind SEQ ID NO: 4 or the polypeptide encoded by SEQ ID NO: 3, antibodies, hybridomas, and compositions thereof, as well as methods of making the antibodies and cell lines that express said antibodies. The language of said claims encompasses all monoclonal antibodies which can recognize a polypeptide that shares 90% or greater homology with SEQ ID NO: 4. The specification teaches that SEQ ID NO: 4 is a MCP-1 receptor, a member of the CCR family of receptors.

12. Said claims broadly recite all polypeptides which share at least 90% or greater homology to SEQ ID NO: 4. Since the specification fails to provide any guidance for the successful creation of antibodies against polypeptides which are not SEQ ID NO: 4 but still are a MCP-1R with the claimed properties since protein biochemistry is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation.

13. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to successfully make antibodies with the desired specificity and properties such as neutralizing MCP-1 activity as the art recognizes several receptors which interact with MCP-1 (see art below). Additionally, a person skilled in the art would recognize that predicting the efficacy of using an antibody on a variant of SEQ ID NO: 4 based solely on its sequence homology is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of making such antibodies, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;

(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

14. The following references are cited herein to illustrate the state of the art of homology based predictions and antibody production.

15. The art teaches that CCR2 family members and MCP-1 are involved in some diseases and disorders, however, the Applicant has failed to demonstrate a nexus between SEQ ID NO: 4 and a particular disorder or disease such that a pharmaceutical compositions would be enabled for use [see Maus *et al.* (1 August 2002) "The Role of CC Chemokine Receptor 2 in Alveolar Monocyte and Neutrophil Immigration in Intact Mice." Am. J. Crit. Care Med. **166**(3): 268-273, Mack *et al.* (2001) "Expression and Characterization of the Chemokine Receptors CCR2 and CCR5 in Mice." Journal of Immunology **166**: 4697-4704, and Huang *et al.* (19 March 2001) "Absence of Monocyte Chemoattractant Protein 1 in Mice Leads to Decreased Local Macrophage Recruitment and Antigen-Specific T Helper Cell Type I Immune Response in Experimental Autoimmune Encephalomyelitis." J. Exp. Med. **193**(6): 713-725].

16. The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that

differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly small peptides, conjugation appears to be required for promoting an effective immune response. Furthermore, US 2002/0150877 A1 (17 October 2002) Augustus discloses a polypeptide (SEQ ID NO: 325) which shares 98.2% sequence homology with SEQ ID NO: 3, but US 2002/0150877 teaches that SEQ ID NO: 325 is a cancer related gene, not necessary a CCR2 (paragraph [0014]). Thus the skilled artisan is presented with a level of unpredictability if polynucleotides which share high sequence homology with SEQ ID NO: 3 can encode different proteins and hence give rise to false positive results with antibodies.

17. Further Regarding derivatives and fragments of SEQ ID NO: 4 and SEQ ID NO: 3 encoded polypeptides, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. For instance, Hemmerich *et al.* (15 September 1999) "Identification of Residues in the Monocyte Chemotactic Protein-1 That Contact the MCP-1 Receptor, CCR2." Biochemistry **38**: 13013-13025 teaches that point mutations in a CCR2 in a critical area can abolish its ligand binding (Figures 1 and 3). Thus a single amino acid change can ruin the binding specificity as required by the instant claims.

18. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be

made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1): 34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al.,

1996, Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

19. Also, claim 15 is drawn to production of an antibody or antigen binding fragment in a prokaryotic cell line. While there is adequate support in the specification and prior art for the expression of MCP-1R, no guidance or examples are given to the expression of an antibody or antigen binding fragment in a prokaryotic cell line.

20. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would require the identification, cloning, and characterization of polypeptides with 90% homology to SEQ ID NO: 4 that retain the claimed properties. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

21. Claims **2-19** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

22. The claims are drawn to antibodies or antigen binding fragments that bind to polypeptides having at least 90% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity.

23. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 4. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

24. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

25. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

26. Therefore, only isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 4, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

27. Claims **2** and **3** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

28. The term "specifically" in claims 2 and 3 is a relative term which renders the claim indefinite. The term "specifically" is not defined by the claim, the specification does not provide

a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

29. Claims **13, 14**, and **15** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

30. Claim 13 recites the limitation "the monoclonal antibody" in first line. There is insufficient antecedent basis for this limitation in the claim.

31. Claims 14 and 15 recite the limitation "the cell line" in the first line. There is insufficient antecedent basis for this limitation in the claim.

Summary

32. The following articles and patents were found by the Examiner during the art search and are here made of note:

a. US 6403767 B1 (11 June 2002) Graham *et al.* (SEQ ID NO: 50 of US '767 shares 100% homology with SEQ ID NO: 4).

b. US 5776729 (7 June 1998) Soppet *et al.* (SEQ ID NO: 3 of US '729 shares 96.7% homology with SEQ ID NO: 4).

c. US 6084075 (4 July 2000) Lind *et al.*

d. US 6312689 B1 (6 November 2001) LaRosa

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
June 4, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER